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Low dose typical antipsychotics – a brief evaluation

Atypical antipsychotics have, according to some, revolutionised the treatment of schizophrenia. These drugs are claimed to be better tolerated than older typical drugs largely because of their lower propensity to cause acute extrapyramidal side-effects (EPSE). Some atypicals cause little or no hyperprolactinaemia. Some are suggested to cause less tardive dyskinesia than typical drugs. Many are claimed to improve, to a relatively greater extent, negative and cognitive symptoms of schizophrenia. In addition, one atypical, clozapine, is unarguably more effective than typical drugs in the treatment of refractory schizophrenia. Atypical drugs are now sometimes recommended as first choice treatment for schizophrenia (Lieberman, 1996; Taylor *et al*, 2000).

Set against these positive views are the draft recommendations of the National Schizophrenia Guidelines Group of the Royal College of Psychiatrists. This group apparently suggests that typical drugs should be first choice agents (Donnelly, 1999) on the basis that atypical drugs have only been compared with moderate or high doses of typical drugs and not with lower doses, which might be relatively better tolerated (Bebbington, 1999). The essence of this argument is that typical antipsychotics are effective and well-tolerated when used in low doses.

In order to evaluate properly this interesting proposition, it is necessary to define very carefully the terms used. What is meant, for example, by 'low doses'? Most trials of atypical drugs used for comparison fixed doses of haloperidol of 10 mg or 20 mg a day. Where dose titration was allowed, mean doses of haloperidol were between 10 mg and 20 mg/day. 'Low dose' therapy, therefore, is assumed to indicate a dose of less than 10 mg a day of haloperidol. 'Effective' might be taken to mean unequivocally more effective than placebo as measured by recognised rating scales. 'Well-tolerated' could be assumed to indicate placebo levels of EPSE, hyperprolactinaemia and tardive dyskinesia. Thus, the central question is this – is there a dose of typical antipsychotic that is effective, but does not give rise to typical adverse effects?

Additional complications to this conundrum are the doses of typical drugs used in practice and whether or not these reflect doses used in clinical trials. Alongside this, it is also important to consider the adverse effect burden induced by normal clinical use of typical drugs. That is, how toxic are atypicals when used in clinician-determined doses?

Clinical dosing and adverse effect burden

A large number of studies have examined adverse effects induced by typical drugs in clinical practice. For example, in a cohort of subjects given, on average, the equivalent of 24 mg/day haloperidol[1], Richardson and Craig (1982) noted high levels of adverse effects despite the use of anticholinergic medication. Of 132 patients examined, 19.7% had parkinsonism-like symptoms and 28% tardive dyskinesia. In a Japanese cohort receiving the equivalent of 64 mg/day haloperidol, 34.8% of patients showed signs of tardive dyskinesia and 40.5% had parkinsonism (Binder *et al*, 1987). Similar findings were reported for a sample of patients in Scotland (McCreadie *et al*, 1992): 29% had tardive dyskinesia, 27% parkinsonism and 23% akathisia (mean dose approximately equivalent to 10 mg/day haloperidol). More recently, a large (*n*=1559) Italian survey found 29.4% of patients suffering EPSE (mostly parkinsonism) and 18.3% with persistent tardive dyskinesia. In that survey, more than 75% of patients were prescribed doses equivalent to, or less than, 10 mg/day haloperidol (Muscettola *et al*, 1999).

In each of these surveys, free use of anticholinergic medication was allowed. Although this might be expected to reduce the prevalence of EPSE, it clearly does not suppress symptoms in all cases. Prophylactic treatment with anticholinergics is also, it seems, only partly effective (Keepers *et al*, 1983).

It is clear then that EPSE and tardive dyskinesia are commonly seen in patients prescribed typical drugs at a wide range of clinically determined doses. It is also likely that, in practice, the prevalence of these effects is underestimated: patient and prescriber experiences and expectations differ widely (Day *et al*, 1998), and training in detection of adverse effects effectively doubles observed prevalence of some adverse effects (Chaplin *et al*, 1999).

1. In all cases, haloperidol 2.5 mg has been assumed to be equivalent to 100 mg/day chlorpromazine or chlorpromazine equivalents.

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Typicals and EPSE – inexorably linked?

Clinical trials

Can typical drugs be prescribed such that EPSE do not occur? Surprisingly, there has been little work done specifically to address this question, but a number of studies have examined the therapeutic and (less systematically) adverse effects of low dose typicals, particularly haloperidol.

An early study by Ayd (1972) evaluated haloperidol and fluphenazine at a mean dose of 3.4 mg/day. Both drugs were effective at this dose, but 10/23 subjects suffered EPSE and six of them were withdrawn from treatment. Later, Van Putten et al (1990) evaluated three doses of haloperidol (5 mg, 10 mg and 20 mg/day). The highest dose was marginally the most effective, but caused relatively more severe akinesia and akathisia. The 10 mg/day and 5 mg/day doses caused similar rates of these adverse effects and were equally effective. A similar study (Levinson et al, 1990) used three doses of fluphenazine (10 mg, 20 mg and 30 mg/day) and found that doses above 0.2 mg/kg were associated with clinical improvement *and* a high incidence of EPSE: the two outcomes could not be separated by dose. One further fixed-dose study (Rifkin et al, 1991) found haloperidol 10 mg/day to be just as effective as 30 mg/day and 80 mg/day, but no better tolerated.

In an unusual study, McEvoy and colleagues (1991) established the mean threshold for EPSE in a cohort comprising first episode and relapsed schizophrenia. Subjects were given haloperidol 2 mg/day and the dose increased until rigidity appeared or worsened, or until 10 mg/day was reached. (The dose was reduced to 1.0 mg/day or 0.5 mg/day if severe rigidity occurred at 2 mg/day.) This 'neuroleptic threshold' was, essentially, the dose at which EPS appeared. On average, the dose of haloperidol required to induce EPS was 3.7 mg/day (range: 0.5 mg–10 mg/day). Those previously exposed to neuroleptics required 4.3 mg/day (0.5 mg–10 mg/day), whereas first episode neuroleptic-naïve subjects required only 2.1 mg/day (0.5–4 mg/day). These doses were maintained and response was good (44% were rated as responders after 2 weeks) and was not improved by systematic dose increases. Of those maintained on threshold doses, only 4% withdrew because of severe EPSE. Overall, this study clearly showed that EPSE are induced by very low daily doses of haloperidol, but that these doses appeared to be optimally therapeutic. EPSE and therapeutic effects could not be separated, since all subjects experienced EPSE according to the trial protocol.

The most recent fixed-dose uncontrolled study was that of Stone and co-workers (1995). Subjects were given haloperidol 4 mg, 10 mg or 40 mg/day and evaluated for 2 weeks (*n*=15). Subjects given 4 mg/day did just as well as those given higher doses, but no patient prescribed 4 mg or 10 mg/day haloperidol experienced 'severe EPSE'. This small short study provides some evidence to support the use of 4 mg/day haloperidol as a therapeutic dose, but gives little information on toxicity on this dose

(patient numbers were small and treatment duration only 2 weeks).

In contrast to these findings are the results of perhaps the best designed, if inadvertent, study of low dose haloperidol (Zimbroff et al, 1997). Ironically, this trial was intended to evaluate the efficacy of sertindole. Nearly 500 patients with schizophrenia were enrolled and received one of three doses of sertindole, one of three doses of haloperidol (4 mg, 8 mg or 12 mg/day) or placebo. Haloperidol 4 mg/day was not convincingly effective in this study: compared with placebo, this dose was not more effective as measured on the Clinical Global Impression Scale and the positive sub-scale of the Brief Psychiatric Rating Scale. However, all three doses of haloperidol produced similar levels of EPSE (about 40% required anticholinergic drugs) and all doses, including 4 mg/day, produced substantially and significantly more EPSE than placebo. It can be seen then, that in this study 4 mg/day haloperidol was not convincingly effective, while producing levels of EPSE no different from higher doses. This strongly supports the contention that EPSE appear at essentially sub-therapeutic doses of haloperidol and is, for the most part, in accord with other data presented here.

Plasma level studies

Prescribed dose is an inexact predictor of drug plasma level obtained because metabolism and distribution of antipsychotics vary widely. Several trials have attempted to establish a threshold plasma level for therapeutic response (Van Putten et al, 1992; Levinson et al, 1995; Volvavka et al, 1995; Palao et al, 1996), but none determined a level at which therapeutic effects occurred but at which EPSE did not. In fact, one trial (Levinson et al, 1995) found therapeutic response to be optimal and EPSE marked at plasma levels above 1.0 mg/ml, so clearly linking the two effects.

Receptor binding studies

Neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow estimates to be made of drug receptor occupancies in the striatum. Typical drugs appear to induce EPSE at striatal occupancies of D_2 receptors of around 75%, which are afforded by doses of around 4 mg/day haloperidol (Farde et al, 1992). Two small studies (total *n*=9) have reported clinical effectiveness at occupancies lower than 75% (Kapur et al, 1996; Hirschowitz et al, 1997). In the larger study (Kapur et al, 1996), five out of seven first-episode subjects responded to 2 mg haloperidol and showed mean striatal occupancies of 67%. Two subjects suffered very mild EPSE. In the smaller study, two subjects with 'minimal prior antipsychotic treatment' were given 2 mg/day and 4 mg/day haloperidol. Both patients responded and showed receptor occupancies of 51% and 72%, respectively. Only the subject given 2 mg/day haloperidol showed any signs of EPSE – mild akathisia and reduced arm swing.

These studies tentatively suggest that there may be a dose of haloperidol that is effective but does not induce EPSE, and that dose might be guided by neuroimaging trials. However, the studies presented here were small and uncontrolled and, more importantly, subjects showed clear signs of EPSE even at low doses associated with D_2 occupancies below 75%. In addition, the precision and validity of neuroimaging studies have recently been called into question (Seeman & Tallerico, 1999).

Hyperprolactinaemia

It has long been acknowledged that moderate doses of typical antipsychotics (approximately equivalent to 15 mg/day haloperidol) cause symptomatic hyperprolactinaemia (Beumont et al, 1974). The dose required to engender a rise in plasma prolactin has only been superficially examined. Meltzer and Fang (1976) found that the equivalent of 100 mg chlorpromazine given twice daily (equivalent to approximately 5 mg/day haloperidol) caused prolactin to rise within 72 hours in all 27 subjects evaluated. On average, plasma prolactin increased almost fourfold and closely paralleled clinical response. Later, Nishikawa and co-workers (1985) showed that pimozide 2 mg/day and thioridazine 75 mg/day were subtherapeutic but clearly raised plasma prolactin (by about 25–100%). Higher doses of pimozide (6 mg/day, equivalent to 6 mg/day haloperidol) were effective but increased plasma prolactin by approximately 400%. More recent studies suggest that prolactin levels begin to rise after as little as 0.5–1.5 mg haloperidol and that hyperprolactinaemia is an unavoidable consequence of the therapeutic use of typical drugs (Hamner & Arana, 1998).

Tardive dyskinesia

Tardive dyskinesia is a well-recognised long term adverse effect of typical antipsychotics. The risk of tardive dyskinesia seems to be associated with drug dose (Morgenstern & Glazer, 1993; Chakos et al, 1996) and duration of treatment (van Os et al, 1997). There appears to be no trial that examined the threshold dose at which the incidence of tardive dyskinesia is increased over that of placebo. However, a number of trials in older patients have shown that tardive dyskinesia is apparently induced by doses less than 4 mg/day haloperidol equivalents (Toenniessen et al, 1985; Caligiuri et al, 1997; Jeste et al, 1999). Thus, a 'safe' therapeutic dose of typical antipsychotics has not been established and, according to limited evidence, may not exist.

Conclusions

Typical antipsychotics appear to be widely used in moderately high doses, which are associated with high prevalences of acute and chronic movement disorders. Trials of lower doses of typical drugs generally indicate that clinically relevant EPSE occur at daily doses that are not clinically effective or at the lower end of the effective dose range. Both hyperprolactinaemia and, less convin-

cingly, tardive dyskinesia appear to be engendered by essentially sub-therapeutic doses of typical agents.

It should be noted, however, that this paper is a brief review based on a simple Medline search conducted in January 2000. As such, it may represent a selective review of relevant literature. In addition, the use here of haloperidol as the 'standard' typical may also be partly misrepresentative: butyrophenones are accepted to produce relatively high rates of movement disorder.

Nevertheless, the trials presented here indicate that, in relapsed schizophrenia, the effective dose of haloperidol is more than 4 mg/day. Four very comprehensive reviews support this suggestion (Baldessarini et al, 1988; Kane & Marder, 1993, 1995; Bollini et al, 1994). It appears that EPSE occur at doses of 4 mg haloperidol or less and that hyperprolactinaemia is induced by doses even lower than this one. We can only conclude, therefore, that typical antipsychotics cannot be used effectively without giving rise to typical adverse effects. Moreover, low but effective doses seem to cause as many 'typical' adverse effects as higher doses such as those used in the trials of atypical drugs. Low-dose typical antipsychotics seem to offer little or no advantage over higher doses.

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